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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,233	01/18/2006	Rodney B. Croteau	4630-66380-05	3606

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,233	CROTEAU ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7-10,16,19-21,27 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,3,5,7-10,13,14,16,19-21,24,25,27,29-32,35,36,38,41,43,47,49-53,55-58,60 and 63.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,3,13,14,24,25,29,35,36,38,41,43,47,49-53,55-58,60 and 63.

DETAILED ACTION

This application is a 371 of PCT/US04/23656.

The preliminary amendment filed on January 18, 2006, canceling claims 2, 4, 6, 11-12, 17-18, 22-23, 26, 28, 33-34, 37, 39-40, 42, 44-46, 48, 54, 59, 61-62 and 64-65 and amending claims 5 and 7, has been entered. The amendment contains no new matter.

Claims 1, 3, 5, 7-10, 13-14, 16, 19-21, 24-25, 27, 29-32, 35-36, 38, 41, 43, 47, 49-53, 55-58, 60 and 63 are pending. Claims 1, 3, 13-14, 24-25, 29, 35-36, 38, 41, 43, 47, 49-53, 55-58, 60 and 63 are withdrawn. Claims 5, 7-10, 16, 19-21, 27 and 30-32 are under consideration.

Election/Restrictions

Applicant's election without traverse of Group II (claims 5, 7010, 13-14, 16, 19-21, 24-25, 27, 30-32 and 35-36) in the reply filed on September 10, 2007 is acknowledged.

Examiner inadvertently placed claims 13-14, 24-25 and 35-36, drawn to a transgenic organism, into Group II. Claims 13-14, 24-25 and 35-36 should have been placed into a separate group since transgenic organisms are patentably distinct from polynucleotides or cells transformed with said polynucleotides. During a telephone conversation with Ms. DeGrandis on September 20, 2007, applicants elected to continue prosecution of Group II now drawn to claims 5, 7-10, 16, 19-21, 27 and 30-32.

Claims 1, 3, **13-14, 24-25**, 29, **35-36**, 38, 41, 43, 47, 49-53, 55-58, 60 and 63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 10, 2007.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on January 18, 2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and claim 16 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the phrase "as set forth in". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner if the recited nucleic acid molecule has the nucleic acid sequence of SEQ ID NO:1 or is a representative member of a genus. Examiner suggests amending the phrase as "the

sequence of SEQ ID NO:1" to clearly indicate that the nucleic acid molecule comprises the sequence of SEQ ID NO:1.

Claim 16 and claims 19-21 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Claim 16 recites the phrase "hybridizes under high stringency conditions". The metes and bounds of the phrase are not clear in the context of the claims. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. Therefore, it is not clear to the Examiner as to what hybridization conditions are encompassed in the phrase. Examiner requests clarification of the above phrase. For examination purposes, Examiner has interpreted the phrase broadly to encompass a hybridization condition of hybridizing at 5X SSC at 65° with a wash at 2XSSC at room temperature. However, if applicants' intended meaning of the phrase is different from the examiner's interpretations as stated above, applicants are requested to so state and clarify the record.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 7-10, 16, 19-21, 27 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide

encoding a polypeptide having the amino acid sequence of SEQ ID NO:2 and having taxoid oxygenase activity, vector comprising said polynucleotide and a cell transformed with said polynucleotide, does not reasonably provide enablement for a polynucleotide having any structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to **(1)** a polynucleotide encoding a polypeptide having at least 80% sequence identity to SEQ ID NO:2 and having taxoid oxygenase activity, **(2)** a polynucleotide having at least 80% sequence identity to SEQ ID NO:1 and encoding a polypeptide having taxoid oxygenase activity, **(3)** a polynucleotide that hybridizes to a nucleic acid probe comprising at least 600 base pairs of the polynucleotide of SEQ ID NO:1, wherein the polynucleotide encodes a polypeptide having taxoid oxygenase activity and **(4)** a recombinant molecule comprising a promoter sequence linked to the polynucleotide of (1), (2) or (3), and **(5)** plant cell, insect cell, bacteria or yeast cell transformed with the recombinant molecule of (4).

The breadth of the claims.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." Regarding claims 16 and 19-21, Examiner has interpreted the phrase "hybridizes under high stringency conditions" to broadly to encompass a hybridization condition of hybridizing with a wash of 2XSSC at room temperature. Also, it is noted that Examiner has used the conventional formula for determining the Tm (Meinkoth et al. Anal. Biochem. 138, 26 (1984) – form PTO-892). According to the formula of Meinkoth et al., (page 269), T_m = 81.5 +16.6(log10 M) + 0.41(%GC) - 0.61 (% formamide) - 500/Length in bp, in a wash solution comprising 1X SSC (M=0.330), G+C content of 49% (359C and 463 G), and a probe of 600 bp, the T_m of perfect hybrids would be 74°C. The recited hybridization wash is at room temperature, 25°C, which allows for 49% base pair mismatch or polynucleotide sequences that have about 51% sequence identity to SEQ ID NO:1. Therefore, the claims are drawn to a polynucleotide having at least 80% sequence identity to SEQ ID NO:1, including any or all recombinants, variants and mutants thereof, and encoding polypeptides having at least 80% sequence identity to SEQ ID NO:2 and having taxoid oxygenase activity and a polynucleotide hybridizing to any 600 base pairs of SEQ ID NO:1 under the above hybridization condition, which encompasses polynucleotides having 51% sequence identity to SEQ ID NO:1, including any or all recombinants, variants and mutants thereof, which encode polypeptides having taxoid oxygenase activity.

Therefore, the claims encompass polypeptides having any structure. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides of virtually any structure. In the instant case, the specification enables a polynucleotide of SEQ ID NO:1 that encodes a polypeptide having the amino acid sequence of SEQ ID NO:2 and having taxoid oxygenase activity.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.

While nucleic acid/enzyme isolation techniques, recombinant and mutagenesis techniques were known in the art at the time of the invention, e.g. hybridization or mutagenesis, and it is routine in the art to screen for variants comprising multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, while the skilled artisan can produce polynucleotides having the recited structural characteristics using well-known and widely used techniques in the art, the amount of experimentation required is not routine due to the fact that the number of species encompassed by the claims is extremely large. For example, Guo et al.(*Proc Natl Acad Sci USA*. 2004 Jun 22;101(25):9205-10

– form PTO-892) teaches that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% (*x* factor) and that this number appears to be consistent with other studies in other proteins as well (Abstract). Guo et al. further shows in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ x 100% where x is the number of mutations introduced and 0.66 is the probability of a protein to remain active after one amino acid change (0.66= 1-0.34). If one were to apply this estimate to the instant case, for polynucleotides encoding polypeptides having 80% sequence identity to SEQ ID NO: 2 (502 amino acids; 100 mismatches = 0.20 x 502), only $(.66)^{100}$ x 100% or 9.0 x 10^{-17}% of random mutants having 80% sequence identity to SEQ ID NO:2 would be active. As indicated above, 80% sequence identity to SEQ ID NO: 2 allows for 100 amino acid changes. Therefore, to find a single active mutant within random mutants having 80% sequence identity to SEQ ID NO: 2, one of skill in the art would have to screen close to a gargantuan number of mutants (100/9.0 x 10^{-17}%). For a polypeptide encoded by a polynucleotide having 51% (see above calculation) sequence identity to SEQ ID NO:2, (502 amino acids; 246 mismatches = 0.49 x 687) only $(.66)^{246}$ x 100% or 4.1 x 10^{-43}% of random mutants having 51% sequence identity to SEQ ID NO: 2 would be active. As indicated above, 51% sequence identity to SEQ ID NO: 2 allows for 246 amino acid changes. Therefore, to find a single active mutant within random mutants having 51% sequence identity to SEQ ID NO: 2, it would be impossible to one of skill in the art would have to screen such a gargantuan number of mutants (100/4.1x 10^{-43}%).

Therefore, in the absence of: (a) rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function, (b) a correlation between structure and taxoid oxygenase activity, the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. One of skill in the art would have to test these infinite possible polynucleotides to determine (1) which ones encode polypeptides having taxoid oxygenase activity, (2) the specific substrates targeted by such proteins and (3) how to use those polynucleotides encompasses by the claims which do not encode polypeptides having taxoid oxygenase activity. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance which respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

The state of prior art, the relative skill of those in the art, and predictability or unpredictability of the art.

Since the amino acid sequence of the encoded protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and

detailed knowledge of the ways in which the proteins' structure relates to its function. In the instant case, neither the specification or the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any polypeptides having the same biological function as that of the polypeptide of SEQ ID NO:2 or predict the function of a polypeptide from its primary structure. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within the polypeptides of SEQ ID NO:2 can be modified and which ones are conserved such that one of skill in the art can make the recited polypeptides having the same biological activity as that of the polypeptide of SEQ ID NO:2, (2) which segments of the polypeptide of SEQ ID NO:2 are essential for activity, and (3) the general tolerance of taxoid oxygenase proteins to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules

of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions.

The amount of direction or guidance presented and the existence of working examples.

The specification discloses only a polynucleotide of SEQ ID NO:1 encoding a polypeptide of SEQ ID NO:2 which has taxoid oxygenase activity. However, the speciation fails to provide any information as to (1) specific substrates associated with the taxoid oxygenase of SEQ ID NO:2, (2) structural elements required in a polypeptide having taxoid oxygenase activity, or (3) which are the structural elements in the polypeptide of SEQ ID NO:2 hat are essential to display taxoid oxygenase activity. No correlation between structure and function of having taxoid oxygenase activity has been presented. There is no information or guidance as to which amino acid residues in the polypeptide of SEQ ID NO:2 can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability of the prior art in regard to structural changes and their effect on function and the lack of knowledge about a correlation between structure and function, an undue experimentation would be necessary one having ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of

enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides having the desired biological characteristics recited in the claim is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5, 7-10, 16, 19-21, 27 and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Croteau et al.

Claims 5, 7-10, 16, 19-21, 27 and 30-32 are drawn to **(1)** a polynucleotide encoding a polypeptide having at least 80% sequence identity to SEQ ID NO:2 and having taxoid oxygenase activity, **(2)** a polynucleotide having at least 80% sequence identity to SEQ ID NO:1 and encoding a polypeptide having taxoid oxygenase activity, **(3)** a polynucleotide that hybridizes to a nucleic acid probe comprising at least 600 base pairs of the polynucleotide of SEQ ID NO:1, wherein the polynucleotide encodes a polypeptide having taxoid oxygenase activity and **(4)** a recombinant molecule comprising a promoter sequence linked to the polynucleotide of (1), (2) or (3), and **(5)**

plant cell, insect cell, bacteria or yeast cell transformed with the recombinant molecule of (4).

Croteau et al. (WO 01/34780 – form PTO-892) discloses a polynucleotide which encodes a polypeptide having taxoid oxygenase, wherein said polynucleotide is 85% identical to SEQ ID NO:1 of the instant invention and wherein the encoded polypeptide has 91% sequence identity to SEQ ID NO:2 of the instant invention, a recombinant molecule comprising a promoter sequence linked to said polynucleotide and a plant cell, insect cell, bacteria or yeast cell transformed with said recombinant molecule of (claims 1-10). The polynucleotide of Croteau et al. will hybridize with a probe comprising of 600 base pairs of SEQ ID NO:1 of the instant invention. Therefore, the reference of Croteau et al. anticipates claims 5, 7-10, 16, 19-21, 27 and 30-32

Claims 5, 7-10, 16, 19-21, 27 and 30-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Croteau et al.

Claims 5, 7-10, 16, 19-21, 27 and 30-32 are drawn to **(1)** a polynucleotide encoding a polypeptide having at least 80% sequence identity to SEQ ID NO:2 and having taxoid oxygenase activity, **(2)** a polynucleotide having at least 80% sequence identity to SEQ ID NO:1 and encoding a polypeptide having taxoid oxygenase activity, **(3)** a polynucleotide that hybridizes to a nucleic acid probe comprising at least 600 base pairs of the polynucleotide of SEQ ID NO:1, wherein the polynucleotide encodes a polypeptide having taxoid oxygenase activity and **(4)** a recombinant molecule comprising a promoter sequence linked to the polynucleotide of (1), (2) or (3), and **(5)**

plant cell, insect cell, bacteria or yeast cell transformed with the recombinant molecule of (4).

Croteau et al. (US Patent No. 6,787,343 & US Patent No. 7,005,283 – form PTO-892) discloses a polynucleotide which encodes a polypeptide having taxoid oxygenase, wherein said polynucleotide is 85% identical to SEQ ID NO:1 of the instant invention and wherein the encoded polypeptide has 91% sequence identity to SEQ ID NO:2 of the instant invention, a recombinant molecule comprising a promoter sequence linked to said polynucleotide and a plant cell, insect cell, bacteria or yeast cell transformed with said recombinant molecule of (claims 1-22 of US Patent No. 7,005,283 and Column 25, line 60 through Column 33, line 16 of US Patent No. 6,787,343). The polynucleotide of Croteau et al. will hybridize with a probe comprising of 600 base pairs of SEQ ID NO:1 of the instant invention. Therefore, the reference of Croteau et al. anticipates claims 5, 7-10, 16, 19-21, 27 and 30-32.

Conclusion

Claims 5, 7-10, 16, 19-21, 27 and 30-32 are rejected.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Yong D. Pak
Patent Examiner 1652